A I D S TREATMENT N E W S

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Contents

AIDS Treatment News

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Statement of Purpose:
AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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Kidney, Liver Transplant Study for People with HIV

Atlanta, Baltimore, Boston, Charlottesville, Chicago (2 Centers), Cincinnati, Cleveland, Los Angeles, Miami, New Orleans, New York (2 Centers), Philadelphia (2 Centers), Pittsburgh, San Francisco, Washington DC (2 Centers)

This study of kidney and liver transplantation for persons with HIV, by 19 transplant centers with funding from the U.S. National Institutes of Health, is currently running and is open for new people. Even for patients who do not need a transplant immediately but may need one in the future, it can be important to get into the system now to avoid delays if and when a transplant is necessary. Persons with hepatitis C or hepatitis B are not disqualified and will be considered for this study.

Volunteers must:

* Meet the criteria for transplantation;

* Have a T-cell count greater than 100 (liver transplant) or greater than 200 (kidney transplant);

* Meet HIV viral load criteria depending on which organ is needed;

* Patients with certain opportunistic infections in the past *will* be considered, and need to have a T-cell count above 200;

* Pediatric patients are being enrolled in several centers in cities listed above.

For More Information

Specific site and study information can be found at
http://spitfire.emmes.com/study/htr/About_Us/about_us.html
(might require Internet Explorer browser), or
http://www.clinicaltrials.gov/

Related published literature can be found at
http://spitfire.emmes.com/study/htr/Useful_Links/useful_links.html

A poster at the recent Retroviruses conference reported the pilot study results so far:
Michelle Roland, M.D., Don Stablein, Laurie Carlson, and others. 1- to 3-year outcomes in HIV-infected liver and kidney transplant recipients. 12th Conference on Retroviruses and Opportunistic Infections, Boston, February 22-25, 2005 [abstract 953]. This poster may be available at http://www.retroconference.org.

HIV "New Strain" Story: For More Information

by John S. James

On February 23, 2005 the State of New York Department of Health (DOH) sent to HIV/AIDS service provides a 10-page update on the single case of a patient with multi-drug resistant HIV who progressed rapidly to AIDS. [1] Extensive media coverage had resulted from an earlier DOH press release and press conference less than two weeks before. [2] The February 23 letter noted that as of that date, "no other persons infected with the same strain have been identified." (A report of a similar virus in San Diego turned out to be erroneous.)

The Retroviruses conference (in Boston, February 22-25, 2005) did little to resolve the questions around this case. The conference quickly added a panel of expert speakers who reviewed current knowledge and answered audience questions, but little new information was available.

Most scientists, physicians, and activists are skeptical about whether this case represents a new strain at all, and they agree that we do not yet know if a new public-health threat has been discovered. But new HIV strains develop all the time. More virulent, transmissible, and/or drug-resistant viruses seem inevitable unless we do better in preventing the transmission of HIV. There is widespread agreement among activists and others that social norms must more clearly insist that risking infection of others or of oneself is not acceptable.

At this time the best information source is a Web page of background papers and documents [3] placed online by CHAMP (Community HIV/AIDS Mobilization Project) and TAG (Treatment Action Group). It is available at
http://www.champnetwork.org/index.php?name=newcase

References

(1) http://www.champnetwork.org/media/NYDOHFeb23.pdf

(2) On February 11 The New York City

Department of Health and Mental Hygiene said in a press release, "A highly resistant strain of rapidly progressive human immunodeficiency virus (HIV) has been diagnosed for the first time in a New York City resident who had not previously undergone antiviral drug treatment...." The full early press release (the one that caused the media frenzy) is at http://www.nyc.gov/html/doh/html/public/press05/pr016-05.html

(3) http://www.champnetwork.org/index.php?name=newcase

HIV: More Voluntary Testing Recommended

by John S. James

Two research articles [1,2] and an editorial [3] in the February 10, 2005 *New England Journal of Medicine* suggested that routine HIV testing be expanded outside of high-risk group to the U.S. general population, or to all but those at lowest risk. Current U.S. CDC guidelines recommend routine use of screening in populations with more than 1% of people infected, but the new articles used different statistical analyses of existing data to show that some HIV screening could be cost effective even in populations with only 0.1% infected -- the prevalence of HIV in the entire U.S. population. For the general public, one-time screening would be most important, but testing every five years or every three years may also be justified for many groups. This HIV testing would have to be voluntary (meaning that individuals could refuse to be tested), or some people would avoid medical care for other conditions in order to avoid the test.

Both studies found that "the effects of screening would extend survival by 1.5 years for the average HIV-infected patient" [3] by catching infection earlier when treatment could be more effective. One of the studies also estimated that "routine one-time screening would reduce the annual rate of transmission by slightly more than 20%" [3] -- because many of the estimated 280,000 Americans who today do not know they have HIV would learn about taking precautions, and those who learn they are negative may be more motivated to make sure they stay that way.

This work was completed before the report on the possible HIV "super strain" in one patient in New York City. If a more dangerous virus is in fact spreading in the U.S. (which is not known as of February 2005), expanded testing could help to protect against it.

The editorial notes that new resources will need to be made available. By coincidence, the Early Treatment for HIV Act, recently introduced in Congress, would help people pay for treatment before they become disabled -- an important part of making expanded testing work (see the following article on early Medicaid treatment).

References

1. Paltiel DA, Weinstein MC, Kimmel AD and others. Expanded HIV screening in the United States -- an analysis of cost-effectiveness. *New England Journal of Medicine.* February 10, 2005; volume 352, pages 586-595.

2. Sanders GD, Bayoumi AM, Sundaram V and others. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. *New England Journal of Medicine.* February 10, 2005; volume 352, pages 570-585.

3. Bozzette SA. Routine screening for HIV infection -- timely and cost-effective. *New England Journal of Medicine.* February 10, 2005; volume 352, pages

620-621.

Early Medicaid Treatment: Bipartisan Bill in Senate with 32 Cosponsors, Could Cut HIV Deaths on Medicaid in Half

by John S. James

On February 8, 2005, Senators Gordon Smith, Hillary Clinton, and 30 other cosponsors introduced the Early Treatment for HIV Act (S. 311, known as ETHA). This bill would let states choose to pay for early HIV treatment under Medicaid, instead of waiting until people become disabled due to advanced illness. A study by PricewaterhouseCoopers projected that over 10 years, early treatment would reduce deaths of persons with HIV on Medicaid by 50%, and more than pay for the cost of care by reducing hospitalization and other expenses of serious illness later. Another benefit is that person on antiretroviral treatment become less infectious due to a lower viral load, reducing transmission to others.

The bill expands existing provisions for breast cancer to also include HIV. Under the existing Federal law, early treatment for breast cancer has been implemented by 49 states.

For more information, including a link to the PricewaterhouseCooper study, see an article by Housing Works, http://www.hwadvocacy.com/update/archives/2005/02/early_treatment_1.html

Tat Inhibitors, A New Approach: Interview with Olaf Kutsch, Ph.D.

by John S. James

Years ago Hoffmann-LaRoche (now Roche) developed an experimental drug that blocked the HIV protein Tat in laboratory tests. But it did not work against HIV in patients, for reasons that were then unknown. Though scientists considered this kind of antiretroviral particularly promising, industry largely abandoned it. Despite over 2,500 scientific publications on the HIV tat gene or Tat protein, the knowledge was not translated into practical drug development.

In 2004 GlaxoSmithKline awarded research grants to three scientists working on new treatment approaches. One award, about $83,000, went to Dr. Olaf Kutsch at the University of Alabama at Birmingham, who had helped develop a new laboratory test for Tat inhibitors. This test can tell how fast the inhibitor is working -- which is important, because HIV-infected T-cells do not survive long in the body. Dr. Kutsch suspects that this is one of the reasons the Roche Tat inhibitor worked in the laboratory but not in patients.

We interviewed Dr. Kutsch on January 12, 2005, about his current work and future directions.

AIDS Treatment News: Why would a Tat inhibitor be important?

Dr. Olaf Kutsch: Usually the preferred approach in developing antiretrovirals is to find a drug that specifically targets a

part of the viral life cycle that is unique to the virus. The HIV Tat protein is essential for the virus to reproduce, but is not found at all in uninfected human cells. Tat was recognized early on as an important target, but so far no one has been able to identify a compound that effectively blocks Tat not only in the laboratory, but also in patients.

I became interested in developing cell-based systems for screening large numbers of compounds to look for potential antiretrovirals, based on work done by Dr. RM Anderson at the Imperial College in London. The idea is to look at instantaneous instead of cumulative outcome of inhibition.

Previous systems looked at cumulative inhibition after several days. But in the body, the half-life of an HIV-infected T-cell is less than two days -- though in the laboratory it can stay alive much longer. So in the laboratory, a compound that would suppress HIV after two or three days might look great at day six. But in the body, if it hasn't done its job in two days, history has passed over that inhibitor. It isn't going to work in patients.

We believe, and hope to prove some day, that our system will have higher predictive value for finding Tat inhibitors that actually work as antiretrovirals. It is impossible to prove this today, because so far there is no example of a Tat inhibitor that works in patients.

ATN: How does your system detect if a chemical inhibits Tat?

Dr. Kutsch: Once HIV has infected a cell, it starts to produce new viral parts that then assemble into new viruses. Imagine this virus production to be controlled by something like a dimmer switch that you use at home to control how bright your light is. This viral dimmer element is called a promoter. Tat is what turns the light on -- actually, really bright. We have taken a copy of this dimmer (promoter) and altered it such that it controls the expression of a green fluorescent protein in our cells. These cells also hold an active virus that produces Tat, which now in turn, turns on the expression of green fluorescent protein. In other words, EGFP [enhanced green fluorescent protein] fluorescence is a direct marker of Tat activity. If an inhibitor does not allow Tat to activate the promoter, you see a decrease in the fluorescence signal -- not instantly, but you can calculate back to what is happening with HIV expression. As Tat inhibitors are the only ones that interfere with the HIV promoter in our test, a strong decrease in the fluorescence signal tells us that we have identified a Tat inhibitor.

With this test, if you put the old Roche inhibitor on the cells, for the first two days almost nothing happens. There may be a 20% decline in the signal -- not enough to control the virus. But if you look after 4 or 8 days, as people did previously, you get the same result they did, 80% to 90% inhibition, which would be fine. But then it is too late.

We have developed a system that can screen at least 10,000 chemical compounds in two days. We have access to a chemical library of 100,000 different compounds. If we can get substantial funding we want to test them all. The test itself is cheap compared to other tests, but infrastructure to do the work must be supported.

With the Glaxo grant and some additional funding, scientists here will be able to go through the 100,000 chemicals and pick a diversity set of 5,000 and screen that. This means that compounds will be chosen because they are representative of chemical groups. For every 20 related compounds we would look at one.

I am concerned that if we run only the

5,000 tests, we would have to be lucky to find something. Other work here has shown that extremely small changes in the molecule make all the difference whether it is going to inhibit Tat or not.

If we are lucky, or if we find the money to run the whole 100,000 chemicals in the library, I think we have a good chance to find something. Then the steps are the usual ones -- you would probably need to find an industry partner who is willing to put money on the compound [the Glaxo grant did not require assigning rights to the results, so other companies could be involved]. The toxicity testing and initial human trial evaluation is very expensive, and there is no mechanism to finance that through Federal funding.

If the Condom Breaks: New U.S. Guidelines for Non-Occupational Exposure to HIV

by John S. James

In case of significant accidental exposure to HIV it is important to begin a 28-day course of antiretrovirals immediately to reduce the risk that HIV infection could be established. New (January 20, 2005) U.S. guidelines for preventing HIV infection after exposure through sexual intercourse, sexual assault, injection drug use, or accidents are available at
http://www.aidsinfo.nih.gov/guidelines/
(click "Nonoccupational ..." on the left), or at
http://www.cdc.gov/mmwr/mmwr_rr.html

Most importantly, treatment must begin as soon as possible. After 72 hours is probably too late (although the guidelines note that physicians might consider treatment even after 72 hours "for exposures conferring a serious risk of transmission"). Treatment should begin much earlier than 72 hours if at all possible.

The new guidelines do not specify what drugs should be used, but refers to three-drug combinations recommended for treatment of persons already infected with HIV. The guidelines caution against nevirapine because of its potentially life-threatening side effects in HIV-negative people (when used continuously -- these side effects do not happen from a single dose). And efavirenz should be avoided in pregnant women and "women of childbearing potential" (presumably meaning women who might become pregnant while this drug is in the body).

These nPEP (non-occupational post-exposure prophylaxis) guidelines are similar but not the same as the guidelines for treating healthcare workers exposed by a needlestick or other accident on the job.

New California Guidelines Also

California also issued its own non-occupational post-exposure guidelines recently (both the U.S. and California guidelines had been greatly delayed). A January 27 email update from the American Association of HIV Medicine (AAHIVM) compared the documents as follows:

"The state of California also released its recommendations last week. With two summary tables, patients information sheets, sample scripts about how to address the key issues in PEP and even a sample progress note, they offer a user-friendly, slightly different perspective on some key issues. These issues include: how many medications to use, how many blood tests are needed, and how to think about who is at the greatest risk.

"The California guidelines are available

at http://www.dhs.ca.gov/ps/ooa.

"Critically, both guidelines stress the need for risk reduction counseling and referrals to help people stay HIV negative not only as a result of the presenting exposure, but over the long-term. This is the real opportunity that PEP provides to the individual."

For More Information

For background and Web links on prevention of HIV infection after non-occupational exposure, see "Prophylaxis Following Nonoccupational Exposure to HIV" by Michelle Roland, M.D., published online in HIV InSite Knowledge Base, http://hivinsite.ucsf.edu/InSite?page=kb-07-02-07.

Global Good News: Many More Treated

The number of people receiving antiretroviral treatment in developing countries increased 75% in one year, according to a January 26 report from the United Nations. The report was announced the World Economic Forum in Davos, Switzerland, at a joint press conference of the World Health Organization, the Joint United Nations Programme on HIV/AIDS, the United States Government, and the Global Fund to Fight AIDS, Tuberculosis and Malaria. In sub-Saharan Africa, and in Asia, the number of people on treatment doubled in the last six months of 2004.

This success reflects increased funding from the U.S. PEPFAR program, the Global Fund, and others. It also reflects the determination of many local governments, and the success in rapidly scaling up treatment delivery in countries with little medical infrastructure.

A major problem is the lack of treatment for children, due in large part to the expense and lack of medicine in pediatric liquid form that can be dosed properly. One of six people who die of AIDS are children -- but only one of 20 who get treatment are children.

More progress will also be needed in the three countries that together account for 41% of the total treatment need: India, Nigeria, and South Africa.

A press release on the new report is at http://www.who.int/mediacentre/news/releases/2005/pr07/en/index.html

The full text of the report, "3 by 5" Progress Report: December 2004, can be downloaded at http://www.who.int/3by5/progressreport05/en/

FDA Advisory on Nevirapine

On January 19, 2005, the FDA issued a public health advisory recommending against starting ongoing nevirapine treatment in women with a CD4 count *greater* than 250, unless benefits clearly outweigh risks. Both men and women (but especially women) with a high CD4 count are at greater risk of liver toxicity from nevirapine than those with more advanced HIV disease. This warning is not new; the manufacturer Boehringer Ingelheim warned about the same liver risk in February 2004. The new advisory reflects recent changes to the package insert, and also provides an excellent short summary on risks and benefits of nevirapine. The FDA noted that "serious and fatal liver toxicity has not been reported after single doses of nevirapine" (used to prevent mother-to-infant HIV transmission during